A study of Kampo medicines in a diabetic nephropathy model

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Abstract

The effects of four Kampo medicines, Ompi-to, Hachimi-jio-gan, Keishi-bukuryo-gan and Sairei-to, were investigated in rats with diabetic nephropathy induced by subtotal nephrectomy and injection of streptozotocin. To evaluate their effects on the glycation reaction, excessive activity of the polyol pathway and oxidative stress (abnormal biochemical processes induced by persistent hyperglycemia), we determined levels of the major endproducts of these processes: advanced glycation endproducts (AGEs) and sorbitol in the kidney and lipid peroxidation in the serum. These three processes were all enhanced in rats with untreated diabetic nephropathy. Oral administration of all four medicines significantly lowered AGEs levels. The renal sorbitol concentration was significantly lowered in the Hachimi-jio-gan-, Sairei-to- and Keishi-bukuryo-gan-treated groups compared with the untreated control group. Serum lipid peroxidation was significantly lowered in the Keishi-bukuryo-gan, Ompi-to and Sairei-to groups, while creatinine clearance and urinary protein excretion (parameters of renal function) were ameliorated by Keishi-bukuryo-gan and Hachimi-jio-gan, respectively, indicating retardation of the progression of diabetic nephropathy. These results suggest the potential therapeutic usefulness of Kampo medicines as a treatment for diabetic nephropathy. It is believed that their actions may occur through different mechanisms.

Key words diabetic nephropathy, advanced glycation endproducts, sorbitol, lipid peroxidation, Hachimi-jio-gan, Keishi-bukuryo-gan, rat.

Abbreviations Hachimi-jio-gan (Ba-Wei-Di-Huang-Wan), 八味地黄丸; Keishi-bukuryo-gan (Gui-Zhi-Fu-Ling-Wan), 桂枝茯苓丸; Ompi-to (Wen-Pi-Tang), 温脾湯; Sairei-to (Chai-Ling-Tang), 柴苓湯.

Introduction

Diabetic nephropathy, a kidney disease associated with diabetes mellitus, is one of the most life-threatening complications of persistent hyperglycemia. The number of patients started on dialysis therapy due to diabetic nephropathy is increasing year by year in Japan. Indeed, according to a report by the Japanese Society for Dialysis Therapy, diabetic nephropathy became the main reason for starting dialysis therapy in 1998, when 10,729 out of the total of 30,051 new dialysis patients (35.7%) required dialysis for this reason. Many patients diagnosed as having diabetic nephropathy advance to end-stage renal failure within a few years, and their prognosis is poor even after the introduction of dialysis therapy. As reported by the Diabetes Control and Complication Trial Research Group, there is no effective treatment for diabetic nephropathy except strict glycemic control.[1] Therefore, it would be desirable to develop drugs capable of inhibiting the occurrence and progression of diabetic nephropathy.

Kampo medicines have been used for patients with diabetes and renal disease, and case reports have indicated improvements in their quality of life as well as prolongation of the pre-dialysis stage of diabetic nephropathy.[2] However, it is not clear how the bioactivity of these medicines contributes towards retarding the progression of diabetic nephropathy.

In a previous *in vitro* study, we investigated the effects of 12 Kampo medical preparations on the formation of advanced glycation endproducts (AGEs), which have

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been implicated as a causative factor in diabetic nephropathy. We found that a rhubarb-based preparation and a vascular system disorder-eliminating drug had strong activity compared with aminoguanidine, while a rehmannia root preparation had moderate activity and a bupleurum root preparation had weak inhibitory activity.[3] Nevertheless, the pathogenesis of diabetic nephropathy involves many factors stemming from persistent hyperglycemia. While the production of AGEs is an important pathogenic mechanism,[4] other biochemical processes, such as excessive activity of the polyol pathway, or oxidative stress may also be closely involved.[5,6] Agents such as aminoguanidine, which inhibits AGEs formation, and aldose reductase inhibitors, which improve disorders of polyol metabolism, may produce some improvement in these processes. Natural medicines also have the potential to become effective new therapeutic agents because they are composed of several crude drugs, and therefore exhibit versatile bioactivity. With this in mind, we performed a study in rats with diabetic nephropathy, to examine the possible therapeutic applications of four Kampo medical preparations, Ompi-to (a rhubarb preparation), Hachimi-jio-gan (a rehmannia root preparation), Keishi-bukuryo-gan (a vascular system disorder-eliminating drug) and Sairei-to (a bupleurum root preparation).

Materials and Methods

Preparations : The composition of the Ompi-to used in the experiments was as follows: Rhei Rhizoma (*Rheum officinale* Baillon), 15 g; Ginseng Radix (*Panax ginseng* C.A. Meyer), 3 g; Aconiti Tuber (*Aconitum japonicum* Thunberg), 9 g; Zingiberis Rhizoma (*Zingiber officinale* Roscoe), 3 g and Glycyrrhizae Radix (*Glycyrrhiza glabra* Linn. var. *glandulifera* Regel et Herder), 5 g. As described previously,[7] an extract was obtained by boiling the crude drugs gently in 1,000 ml water for 65 min. This yielded approximately 500 ml of a decoction which was then concentrated under reduced pressure to leave a brown residue, with a yield of about 30% by weight of the original preparation. Extracts for the other medicines were prepared according to the formulae (composition, dosage of each crude drug and production technique, but without any excipients) for the commercial products manufactured by Tsumura Juntendo, Inc., Tokyo, Japan. A specimen of each has been deposited with the Institute of Natural Medicine, Toyama Medical and Pharmaceutical University.

Animals and treatment : Male Wistar rats (Japan SLC, Inc., Hamamatsu, Japan) weighing 160-170 g were kept in a room with automatically controlled temperature (23℃) and humidity (60%) and a conventional lighting regimen (dark at night). According to the method reported previously,[8] the rats underwent resection of half of the left kidney and total excision of the right kidney at 7-day intervals. Thereafter, they were injected intraperitoneally with 35 mg/kg body weight streptozotocin in citrate buffer (10 mM, pH 4.5). Their blood glucose and urea nitrogen levels were determined after recovery from the injection, and they were divided into five groups (a control and four treatment groups), avoiding any intergroup differences in these blood indices. A normal group, in which the rats underwent a sham operation, was also included. Each experimental group contained eight rats. Over the 5-week experimental period, the normal and control groups received plain drinking water, while the four treatment groups were given an oral solution of Ompi-to, Hachimi-jio-gan, Keishi-bukuryo-gan or Sairei-to, respectively, at a dose of 150 mg/kg body weight/day. At the end of the experimental period, the urine was collected and blood samples were obtained by cardiac puncture. The serum was immediately separated from the blood samples by centrifugation. After renal perfusion through the renal artery with ice-cold physiological saline, the kidneys were removed from each rat, frozen quickly and kept at -80℃ until analysis.

Determination of blood and urine components : Glucose, urea nitrogen, creatinine (Cr) and triglyceride (TG) in serum were determined using commercial reagents (Glucose CII-Test Wako and Triglyceride E-Test Wako obtained from Wako Pure Chemical Industries, Ltd., Osaka, Japan; BUN Kainos and CRE-EN Kainos obtained from Kainos Laboratories, Inc., Tokyo, Japan). Glycosylated protein and malondialdehyde (MDA) levels in serum were measured using the methods of McFarland[9] and Naito and Yamanaka,[10] respectively. Urine components were determined as follows: protein by the sulfosalicylic acid method[11] and Cr using a commercial reagent (CRE-EN Kainos obtained from Kainos Laboratories, Inc.). The creatinine clearance (C_{Cr}) was calculated on the basis of urinary Cr, serum Cr, urine volume and body weight using the following equation :

C_{Cr} (ml/min/kg body weight) = {urinary Cr (mg/dl) x urine volume (ml)/serum Cr (mg/dl)} x {1,000/body weight (g)} x {1/1,440 (min)}.

Determination of AGEs : According to the method of Nakayama *et al.*,[12] minced kidney was delipidated with chloroform and methanol (2:1) overnight. After washing, the pellet was homogenized in 1.0 ml 0.1 N NaOH, followed by centrifugation at 8,000 x g for 15 min at 4℃. The amounts of AGEs in these alkali-soluble samples were measured by fluorescence at an emission wavelength of 440 nm and an excitation wavelength of 370 nm against a blank of 0.1 N NaOH solution using a spectrofluorometric detector (Shimadzu RF/550, Kyoto, Japan). A native bovine serum albumin (BSA) preparation (1 mg/ml in 0.1 N NaOH) was used as a reference, and its fluorescent intensity was defined as one unit of fluorescence. The fluorescence values of the samples were measured in arbitrary units (AU) relative to the native BSA preparation.

Assay of the renal sorbitol concentration : The sorbitol concentration in the kidney was assayed according to the method of Shinohara *et al.*[13] Briefly, homogenized kidney tissue was deproteinized with $ZnSO_4$-NaOH. A portion of the deproteinized supernatant was assayed enzymatically based on the conversion of sorbitol to fructose by sorbitol dehydrogenase and nicotinamide adenine dinucleotide (NAD), and the formation of reduced NAD (NADH). The reaction mixture included 0.5 ml 0.33 M Tris-HCl buffer (pH 8.6), 1.0 ml 250 mg/dl NAD, 0.1 ml 0.1 M EDTA and 0.05 ml 40 U/ml sorbitol dehydrogenase. After incubation for 30 min at 37℃, the increase in NADH was assayed spectrofluorometrically (excitation at 365 nm, emission at 450 nm).

Statistics : Values are presented as mean ± S.E. Differences between groups were analyzed by Dunnett's test. Significance was accepted at $p<0.05$.

Results

Body weight, kidney weight and urine volume

Changes in the body weight, kidney weight and urine volume of the rats during the 5-week experimental period are summarized in Table I. The body weight of the control rats with diabetic nephropathy was significantly lower than that of the normal rats, and had decreased by 14.5 g after 5 weeks. However, there were no significant differences between the initial and final body weights in the rats treated with the Kampo medicines. Kidney weight and urine volume were also significantly increased in the diabetic nephropathy controls (reaching 0.99 g/100 g body weight and 130.8 ml/day, respectively), reflecting the presence of renal disease. The administration of Hachimi-jio-gan and Keishi-bukuryo-gan reduced the kidney weight significantly compared with these controls. However, there were no significant differences in urine volume between the control group and the four treated groups.

General biochemical features

Table II shows the effect of each medicinal preparation on the serum and urinary parameters after oral administration. The diabetic nephropathy controls showed a higher blood glucose level than the normal rats. Although hyperglycemia was also apparent in the groups

Table I Body weight, kidney weight and urine volume.

Group	Body weight			Kidney weight (g/100 g B.W.)	Urine volume (ml/day)
	Initial (g)	Final (g)	Gain (g)		
Normal	303.8 ± 6.1	366.2 ± 11.4	62.4 ± 6.7	0.35 ± 0.01	17.7 ± 1.4
Diabetic nephropathy					
Control	246.3 ± 4.8[a]	231.8 ± 10.3[a]	-14.5 ± 6.4[a]	0.99 ± 0.05[a]	130.8 ± 8.7[a]
Ompi-to	247.3 ± 6.8[a]	248.5 ± 9.3[a]	1.3 ± 7.9[a,b]	0.91 ± 0.04[a]	126.3 ± 5.8[a]
Hachimi-jio-gan	247.5 ± 7.9[a]	247.0 ± 15.5[a]	-0.5 ± 9.1[a]	0.90 ± 0.05[a,b]	124.6 ± 4.8[a]
Keishi-bukuryo-gan	255.0 ± 5.6[a]	254.4 ± 13.1[a,b]	-0.6 ± 8.1[a]	0.89 ± 0.04[a,b]	136.4 ± 9.1[a]
Sairei-to	245.3 ± 5.4[a]	240.7 ± 12.0[a]	-5.9 ± 11.3[a]	0.92 ± 0.04[a]	129.7 ± 5.6[a]

Statistical significance: [a]$p<0.001$ vs. normal rats, [b]$p<0.05$ vs. control rats with diabetic nephropathy.

Table II General biochemical features.

Group	s-Glucose (mmol/l)	s-Glycosylated protein (nmol/mg protein)	s-Urea nitrogen (mg/dl)	s-Cr (mg/dl)	C_{Cr} (ml/min/kg B.W.)	s-TG (mg/dl)	u-Protein (mg/day)
Normal	11.7 ± 0.4	12.4 ± 0.8	22.1 ± 0.9	0.38 ± 0.01	5.47 ± 0.25	48.3 ± 5.3	10.7 ± 1.4
Diabetic nephropathy							
Control	41.2 ± 1.9[a]	23.3 ± 1.6[a]	61.5 ± 6.2[a]	0.67 ± 0.03[a]	3.39 ± 0.22[a]	571.5 ± 149.3[a]	92.5 ± 14.0[a]
Ompi-to	36.0 ± 1.6[a,d]	21.0 ± 0.8[a,b]	55.8 ± 2.7[a]	0.64 ± 0.03[a]	3.39 ± 0.21[a]	328.2 ± 43.0[a,d]	89.9 ± 7.1[a]
Hachimi-jio-gan	31.1 ± 1.3[a,d]	20.3 ± 1.0[a,c]	54.7 ± 1.9[a]	0.62 ± 0.02[a]	3.75 ± 0.18[a]	264.1 ± 51.0[a,d]	71.2 ± 15.7[a,b]
Keishi-bukuryo-gan	32.6 ± 1.8[a,d]	19.2 ± 0.7[a,d]	52.7 ± 3.1[a,c]	0.63 ± 0.05[a]	4.13 ± 0.36[a,c]	307.1 ± 86.5[a,d]	83.0 ± 12.9[a]
Sairei-to	32.9 ± 1.8[a,d]	19.7 ± 1.4[a,d]	51.4 ± 4.0[a,c]	0.66 ± 0.05[a]	3.61 ± 0.34[a]	311.7 ± 75.1[a,d]	79.3 ± 17.0[a]

Statistical significance: [a]$p<0.001$ vs. normal rats, [b]$p<0.05$, [c]$p<0.01$, [d]$p<0.001$ vs. control rats with diabetic nephropathy.
Abbreviations: s-, serum; u-, urinary; Cr, creatinine; C_{Cr}, creatinine clearance; TG, triglyceride; B.W., body weight.

receiving the Kampo medicines, their glucose levels were significantly decreased ($p<0.001$) compared with those of the diabetic nephropathy controls. Of the four preparations, Hachimi-jio-gan produced the greatest lowering in glucose levels. The glycosylated protein level was also considerably higher in the diabetic nephropathy controls than in normal rats. Following administration of the four Kampo medicines, this parameter behaved in a similar way to glucose, with significant differences from the value in the controls. Urea nitrogen and Cr levels were increased to 61.5 mg/dl and 0.67 mg/dl, respectively, in the control rats. In contrast, this group showed a significant decrease in C_{Cr} compared with the normal rats (from 5.47 to 3.39 ml/min/kg body weight), reflecting the degree of renal dysfunction. The urea nitrogen value was significantly reduced in the rats given Keishi-bukuryo-gan and Sairei-to, and the C_{Cr} value was significantly increased in those given Keishi-bukuryo-gan. However, the actual serum Cr levels showed no significant improvement after administration of any of the preparations. The TG level was 48.3 mg/dl in the rats without diabetic nephropathy; in the control rats with diabetic nephropathy, it increased markedly and significantly, reaching 571.5 mg/dl. However, this increase was significantly ameliorated in the rats treated with the four Kampo medicines, particularly in those given Hachimi-jio-gan, which showed a TG level of 264.1 mg/dl. Urinary protein excretion in the rats with diabetic nephropathy reached 92.5 mg/day, compared with a level of 10.7 mg/day in normal rats. When the effect of oral administration of the four Kampo medicines was examined, urinary protein excretion was decreased significantly (to 71.2 mg/day) in the Hachimi-jio-gan-treated group.

Serum MDA levels

As shown in Fig. 1, the MDA level in the rats with diabetic nephropathy increased to 4.01 nmol/ml, reflecting the occurrence of lipid peroxidation. This increment was effectively and significantly suppressed by Ompi-to, Keishi-bukuryo-gan and Sairei-to, although the values were still higher than those in normal rats. In contrast, Hachimi-jio-gan had no effect on MDA.

AGEs levels in the kidney

In comparison with the normal rats, an increase in relative fluorescence (reflecting increased AGEs levels) was observed in the rats that had undergone induction of diabetic nephropathy, as shown in Fig. 2. A clear reduction in the renal AGEs levels was observed in all four Kampo medicine-treated groups, which showed obvious differences from the control rats with diabetic nephropathy.

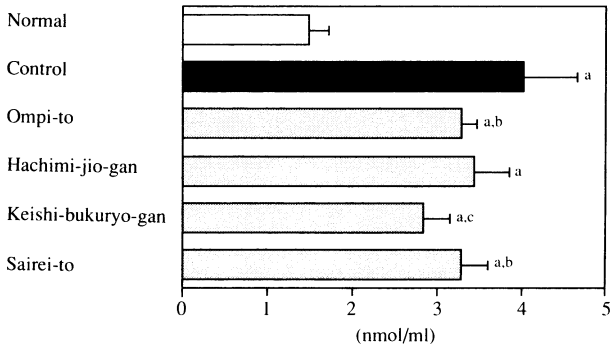

Fig. 1 Serum malondialdehyde (MDA) levels. Statistical significance: [a]$p<0.001$ vs. normal rats, [b]$p<0.05$, [c]$p<0.001$ vs. control rats with diabetic nephropathy.

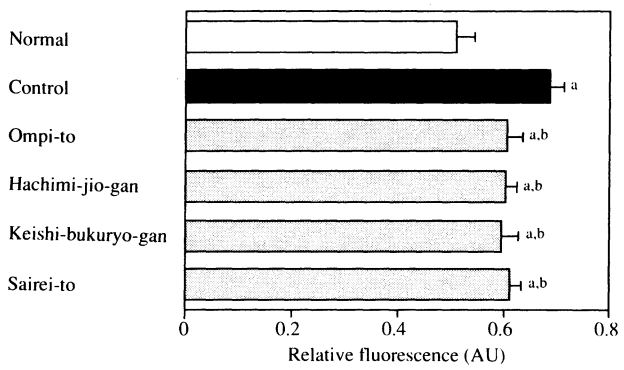

Fig. 2 Advanced glycation endproducts (AGEs) levels in the kidney. Statistical significance: $^{a}p<0.001$ vs. normal rats, $^{b}p<0.001$ vs. control rats with diabetic nephropathy.

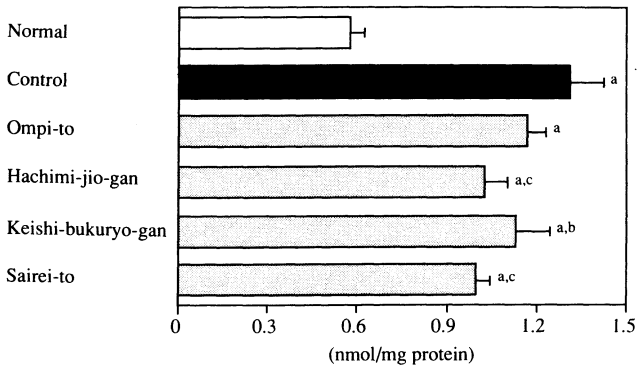

Fig. 3 Sorbitol levels in the kidney. Statistical significance: $^{a}p<0.001$ vs. normal rats, $^{b}p<0.05$, $^{c}p<0.01$ vs. control rats with diabetic nephropathy.

Sorbitol content of the kidney

The changes in the sorbitol content of the kidney following administration of the four Kampo medicines are summarized in Fig. 3. In the control rats with diabetic nephropathy, the renal sorbitol content increased to 1.31 nmol/mg protein. In contrast, the sorbitol content was significantly lower in the rats given Hachimi-jio-gan, Keishi-bukuryo-gan and Sairei-to. This suppression was markedly significant with Sairei-to and Hachimi-jio-gan, while Keishi-bukuryo-gan had a slighter effect.

Discussion

Recent studies have focused on the role of AGEs in the pathogenesis of diabetic nephropathy. AGEs are produced by the protein glycation reaction, which can be broadly divided into the early-phase reaction (in which Amadori rearrangement products are produced) and the late-phase reaction (in which these products are converted to AGEs).[14,15] This reaction is accelerated under hyperglycemic conditions, such as those found in diabetes mellitus. Excessive formation and accumulation of AGEs in the tissues and serum can alter the structure and function of tissue proteins. Vlassara *et al.*[16] demonstrated that chronic administration of AGEs to normal rats leads to pathological changes in the kidney, including increased kidney weight, glomerular hypertrophy, glomerular basement membrane thickening and progressive albuminuria. Moreover, they showed that these pathological changes are ameliorated by aminoguanidine, a known inhibitor of advanced glycation. Therefore, it is important to inhibit the formation of AGEs in diabetes to prevent renal damage. In the present experiment, the level of glycosylated serum protein (the product of the early-phase reaction) was twice as high in control rats as in normal rats. This was mainly a reflection of the high blood glucose levels in the diabetic group. In the groups treated with the four Kampo medicines, these levels were significantly lowered, a trend similar to that seen in blood glucose levels. The amounts of AGEs (the products of the late-phase reaction) were also increased significantly in the kidneys of rats with diabetic nephropathy as measured by fluorescence. All four preparations used in this experiment lowered the levels of fluorescent AGEs to almost identical values, and there were no significant differences between the preparations, different from the *in vitro* data obtained in our previous study.[3] Nevertheless, it is apparent that changes in AGEs levels alone do not exert an influence on blood glucose levels, implying that some other factor(s) must also be involved in the development and progression of diabetic nephropathy.

Other factors that could influence the progression of diabetic nephropathy include oxidative stress and excessive activity of the polyol pathway. In the present study, lipid peroxidation in the serum was 2.7 times higher in rats with diabetic nephropathy than in normal rats. This indicates that there is an increase in oxidative stress in diabetic nephropathy, as has also been shown by other reports.[17,18] This increase in oxidative stress could be partly induced by auto-oxidation of glucose. Recently, it has been demonstrated that the glycation reaction and its products, including both glycated proteins and AGEs, contributes to the production of oxygen free radicals.[19,20] Of the four Kampo medicines tested during the present study, Keishi-bukuryo-gan produced the greatest

lowering of lipid peroxidation, with a 29% decrease. Although Sairei-to produced similar glycemic conditions to Keishi-bukuryo-gan, as assessed by blood glucose and glycosylated serum protein levels, the degree of lipid peroxidation in Sairei-to-treated rats was higher than in those receiving Keishi-bukuryo-gan. Despite achieving the lowest blood glucose level and reducing glycosylated serum protein, Hachimi-jio-gan produced no significant changes in lipid peroxidation, whereas Ompi-to produced a significant decrease despite being associated with higher blood glucose levels than the other three preparations.

Enhanced oxidative stress in diabetes may also result from a dysfunction in the defense system against free radicals, such as a reduction in glutathione due to depletion of the cofactor for NADPH, which is results from activation of the polyol pathway,[5] or inactivation of superoxide dismutase due to protein glycation.[21] We suspect that such factors could have contributed towards the excessive lipid peroxidation seen in our present experiment. Although we cannot propose that antioxidant activity plays a pivotal role in the observed effects of the Kampo medicines tested, Keishi-bukuryo-gan and Ompi-to have been reported to have antioxidant activity, and to scavenge free radicals and inhibit lipid peroxidation *in vitro* and *in vivo*.[22-26] These actions may therefore contribute towards the reduction in lipid peroxidation.

Enhancement of the polyol pathway, leading to the accumulation of sorbitol and fructose in the tissues, has also been proposed to be a causative factor in the development of diabetic nephropathy.[5] The rate-limiting step in this pathway is the reduction of glucose to sorbitol, which is catalyzed by aldose reductase. Sorbitol is subsequently converted to fructose by sorbitol dehydrogenase. Elevated expression of aldose reductase mRNA has been reported to occur in a variety of tissues, including the kidney, under hyperglycemic conditions.[27,28] In addition, Nakamura *et al.* reported that AGEs induce aldose reductase in cultured human microvascular endotherial cells.[29] In the present experiment, renal sorbitol levels were 2.3 times higher than normal in rats with diabetic nephropathy, supporting the theory of excessive activity of the polyol pathway in diabetic nephropathy. Recently, it has been proposed that the polyol pathway may encourage acceleration of the glycation reaction and the production of AGEs by increasing the supply of fructose, which is a reactive glycation agent with a stronger reducing capacity than glucose.[30] Hachimi-jio-gan and Sairei-to lowered sorbitol levels more potently than Ompi-to and Keishi-bukuryo-gan, suggesting that they decrease the fructose concentration in the kidney. This possibility is supported by the observations that Hachimi-jio-gan and Sairei-to improved both blood glucose and AGEs levels in rats with diabetic nephropathy.

Lipid abnormalities are one of the most important complications in patients with diabetes. In the kidney, hyperlipidemia can cause glomerular sclerosis.[31,32] The results of the present study demonstrated that the serum TG level is dramatically increased in rats with diabetic nephropathy. Treatment with the four Kampo medicines revealed a hypolipidemic influence, as reflected by the sharp reduction in TG levels, suggesting a possible therapeutic application.

In this study, measurements of markers of renal disease, including urinary protein excretion and the C_{Cr} (an effective index for expressing the glomerular filtration rate [GFR]), were used to evaluate the progression of diabetic nephropathy. Heavy proteinuria occurred in the rats with diabetic nephropathy, indicating derangement of the selective properties of the glomerular membrane. Proteinuria was reduced by oral administration of Hachimi-jio-gan, which is used clinically in diabetic patients and in all stages of diabetic nephropathy. Sairei-to, which is used in patients with a shorter history of diabetic mellitus, has also been reported to decrease proteinuria in patients with diabetic nephropathy.[33] In the present experiment, Sairei-to decreased the urinary excretion of protein but produced no significant difference between the control and treated groups. The serum urea nitrogen level, which reflects both nitrogen metabolism and the GFR, was decreased in rats with diabetic nephropathy who were given Keishi-bukuryo-gan. The C_{Cr} behaved in a similar way to the serum urea nitrogen. In contrast, Ompi-to did not affect renal function in this study, although it has proved to be useful for chronic renal failure in both clinical studies and animal experiments.[34-36] Our present results, however, seem reasonable because Ompi-to is used clinically in the advanced stages of renal failure and is not used in diabetic patients. Based on the above findings, it can be inferred that Hachimi-jio-gan and Keishi-bukuryo-gan retard the progression of experimentally induced diabetic nephropathy.

However, neither Hachimi-jio-gan or Keishi-bukuryo-gan had any effect on serum Cr levels. More detailed clarification of the renal structural lesions that occur in diabetic nephropathy, such as mesangial expansion and reduction of the glomerular capillary surface area, would be desirable so that this can be explained.

Although further studies will be required to identify the exact role and confirm the usefulness of each of these Kampo medicines as therapeutic drugs for diabetic nephropathy, our data provide some evidence that they have beneficial effects on the metabolic abnormalities induced by persistent hyperglycemia, such as the formation of AGEs, overenhancement of the polyol pathway and oxidative stress. In addition, they produce a sharp reduction in TG levels, suggesting that they have a potential role in attenuating the progression of diabetic nephropathy.

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和文抄録

漢方方剤（温脾湯，八味地黄丸，桂枝茯苓丸，柴苓湯）の糖尿病性腎症に及ぼす影響を，モデルラットを用い検討した。慢性的な高血糖状態では糖化反応，ポリオール経路，酸化ストレスの亢進をひき起こすが，これらの指標の腎組織中の advanced glycation endproducts（AGEs）とソルビトール，血中脂質過酸化量は，いずれも糖尿病性腎症ラットで有意に増加していた。これに対し，4種類の漢方方剤を投与した群では，いずれの場合も腎組織中の AGEs レベルが有意に低下していた。しかしソルビトール含量は八味地黄丸，柴苓湯，桂枝茯苓丸投与群で，血中脂質過酸化量は桂枝茯苓丸，温脾湯，柴苓湯投与群で有意に低下していた。また腎機能パラメーターのクレアチニンクリアランスと尿蛋白排泄量は桂枝茯苓丸，八味地黄丸投与群で有意に改善していた。このことから，4種類の漢方方剤はそれぞれ異なった作用機序で，糖尿病性腎症の進展を抑制している可能性が示唆された。

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